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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/779,957	02/09/2001	Kristi D. Snell	MBX 038	7578

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EXAMINER	
BAUM, STUART F	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/779,957	SNELL, KRISTI D.	
	Examiner	Art Unit	
	Stuart F. Baum	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-16,18 and 20-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6-16,18 and 20-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

RCE Acknowledgment

1. The request filed on January 6, 2004 for a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114, based on parent Application No. 09/779957 is acceptable and a RCE has been established. An action on the RCE follows.

Applicant's arguments and 37 C.F.R. §1.132 Declaration by Kristi D. Snell filed 1/6/2003 have been entered.

2. Claims 1-2, 6-16, 18, and 20-29 are pending.

Claims 3-5, 17, and 19 have been canceled.

Claim 29 has been newly added.

Claims 1-2, 6-16, 18, and 20-29 are examined in the present office action.

Specification

On page 6, line 13, "promoter" is misspelled.

Claim Objections

3. Claims 2 and 16, 2nd line, the recitation "comprises" should be replaced with --comprise-- to correct the grammar.

In claims 2, and 16, eukaryotic is misspelled.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 14 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 14 and 28, the recitation "desirable plant crop traits" is indefinite because Applicants are using this recitation to designate proteins, as is stated in the preamble of the Markush claim, but Applicant has not stated which protein or proteins are required to produce a plant with "desirable plant crop traits". The recitation "desirable plant crop traits" does not specify a particular protein nor group of proteins. It is unclear what protein(s) Applicant is referring to when reciting "desirable plant crop traits".

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-2, 6-16, 18, and 20-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a DNA construct, or a method for expressing multiple genes in cells comprising a DNA construct, comprising a single promoter at the 5' end, multiple genes or exteins encoding one or more proteins, one or more intein sequences, and transcription termination sequences, wherein at least one of the intein sequences can catalyze excision of the exteins and wherein the excised exteins are not ligated, or wherein the DNA construct encodes a glycine or alanine linking the intein and extein amino acid sequences.

Applicant discloses the *Pyrococcus* species GB-D DNA polymerase intein of SEQ ID NO:1 and Applicant further discloses that mutation of the C-terminal "agc" which encodes a serine to a DNA sequence encoding an alanine or glycine, will form a modified intein splicing element that is capable of promoting excision of the polyprotein but will not ligate the extein unit (page 9, 1st full paragraph).

Applicant's claims are drawn to all inteins from all organisms but Applicant has only described one intein sequence from *Pyrococcus* that can be modified and used in Applicant's invention. Applicant has not described a representative number of intein sequences that are operable in Applicant's invention nor any essential regions of an intein that are required for an intein that is operable in Applicant's invention.

The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In summary, the court stated that a written description of an invention requires a precise definition, one that defines the structural features of the chemical genus that distinguishes it from other chemical structures. A definition by function does not suffice to define the genus because it is only an indication of

what the gene does, rather than what it is. The court goes on to say, "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *See University of California v. Eli Lilly and Co.*, 119 F.3d 1559; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Applicant fails to describe a representative number of polynucleotide sequence encoding inteins from a representative number of organisms that when modified are operable in Applicant's invention. Furthermore, Applicant fails to describe structural features common to members of the claimed genus of intein polynucleotides that are required for the intein to operate in Applicant's invention. Hence, Applicant fails to meet either prong of the two-prong test set forth by *Eli Lilly*. Furthermore, given the lack of description of the necessary elements essential for intein function in Applicant's invention, it remains unclear what features identify an operable intein for Applicant's invention. Since the genus of inteins has not been described by specific structural features, the specification fails to provide an adequate written description to support the breath of the claims.

In the "Remarks", filed 1/6/2004, Applicant contends that the specification clearly describes on pages 7-9 how to use available inteins in the claimed method. Applicant contends that the method for making and using the claimed DNA construct is explicity described in Example 1 on page 18 and that the genus of inteins is sufficiently described by the specification and by known databases. Applicant also contends that the intein from Mycobacterium xenopi GyrA also prevents ligation (paragraph bridging pages 13-14).

The Office contends that Applicant's invention does not comprise known inteins but rather inteins that have been modified to work in Applicant's invention. The database of NEB only lists the amino acid sequences of inteins and does not specify which ones would work in Applicant's invention. The Office acknowledges Applicant's disclosure of the intein from Mycobacterium xenopi, but Applicant's contention that said intein will be functional in Applicant's invention is only stated prophetically and is not accompanied by any data.

Scope of Enablement

6. Claims 1-2, 6-16, 18, and 20-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a or a DNA construct, or a method for expressing multiple genes in cells comprising transforming the cells with a DNA construct, comprising a single promoter at the 5' end of the construct, multiple genes or exteins encoding one or more proteins, a modified *Pyrococcus* species GB-D DNA polymerase intein fused to the carboxy-terminus portion of each gene except the last gene to be expressed and a transcription termination sequence wherein the intein sequence catalyzes excision of the exteins and wherein the excised exteins are not ligated, and wherein the DNA construct encodes a glycine or alanine linking the intein and extein amino acid sequences, does not reasonably provide enablement for a DNA construct, or a method for expressing multiple genes in cells comprising a DNA construct comprising any intein sequence from any organism operably linked within the DNA construct as specified above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn to a DNA construct, or a method for expressing multiple genes in cells comprising a DNA construct, comprising a single promoter at the 5' end, multiple genes or exteins encoding one or more proteins, one or more intein sequences, and transcription termination sequences, wherein at least one of the intein sequences can catalyze excision of the exteins and wherein the excised exteins are not ligated, or wherein the DNA construct encodes a glycine or alanine linking the intein and extein amino acid sequences. Applicant further claims that the proteins can be any one of the listed proteins in claims 12-14, or 26-28.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands,* 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

Applicant teaches a DNA construct comprising a promoter operable in plants, an N-terminal extein sequence encoding beta-glucuronidase fused at its C-terminus to the N-terminus of an intein sequence from the *Pyrococcus* species GB-D polymerase in which serine 538 has been mutated to alanine or glycine, a 5'-terminal extein sequence encoding an enhanced green fluorescent protein fused at its 3' terminus to the 5'-terminus of the intein sequence and a polyadenylation signal (paragraph bridging pages 18-19).

Applicants fail to provide guidance for identifying inteins that are operable in Applicant's invention from the multitude of inteins from all organisms. Applicant fails to provide guidance for determining which intein can be modified and still operate in Applicant's invention.

The state-of-the-art teaches posttranslational editing processes that remove an intein from in between separate proteins can produce unpredictable results. Perler (1998, Cell 92:1-4) teaches that there are ten conserved intein motifs, non of which are included in Applicant's claimed invention. Evans et al (2000, The Journal of Biological Chemistry 275 (13): 9091-9094) teach that the number of C-terminal extein amino acid residues has an effect on protein splicing as does the temperature at which the organism is grown (page 9093, right column, 1st and 2nd paragraphs and 4th and 3rd lines from the bottom of the column). Perler teaches that "the *Chlamydomonas eugametos* ClpP intein failed to splice in *E. coli* unless the intein penultimate Gly was mutated to His" (page 1, right column, end of 2nd paragraph). Perler continues by stating that not all inteins work in *E. coli*, "possibly due to misfolding, inhibiting intracellular pH, redox potential, etc" (*supra*) all of which are variables encountered in all living organisms. Perler states that "protein splicing is less efficient when an intein is expressed within a foreign protein", because "proximal foreign extein residues can potentially disturb the intein active-site by steric hindrance" (page 1, 3rd paragraph). Perler concludes by stating "future experiments are also needed to define suitable locations for intein insertion if inteins are to be useful in protein engineering" (*supra).*

In the absence of guidance, undue trial and error experimentation would be required for one of ordinary skill in the art to screen through the multitude of non-exemplified intein sequences from the multitude of organisms, either by using non-disclosed fragments of the

Pyrococcus species GB-D polymerase intein as probes or by designing primers to undisclosed regions of the *Pyrococcus* species GB-D polymerase intein and isolating or amplifying fragments, subcloning the fragments, producing DNA constructs comprising said intein sequence operably associated with two nucleic acid sequences encoding separate proteins and transforming plant cells or bacteria cells therewith, determining if the separate proteins are present in order to identify those, if any, intein sequences that will excise the separate proteins but will not ligate the proteins together.

Therefore, given the breadth of the claims; the lack of guidance and examples; the unpredictability in the art; and the state-of-the-art as discussed above, undue experimentation would be required to practice the claimed invention, and therefore the invention is not enabled.

In the "Remarks", filed 1/6/2004, Applicant contends that the specification teaches how to make the claimed invention including intein sequences that prevent ligation of the cleaved exteins (page 10, 1st paragraph). Applicant contends that the declaration by Dr. Kristi D. Snell demonstrates that making and using the claimed DNA construct is enabled using methods described in the specification (page 10, 2nd paragraph). Applicant contends that the claims define an intein that can catalyze excision of exteins, which is a common feature of all inteins, regardless of the mechanism of action.

The Office contends that Applicant is enabled for a DNA construct comprising the intein from *Pyrococcus* species GB-D polymerase that has been modified to include an alanine or glycine linking the intein and extein amino acid sequences, but, Applicant has not taught how to use all inteins in Applicant's invention, as is claimed. The declaration by Dr. Kristi D. Snell only states that the intein from *Pyrococcus* species GB-D polymerase was used and no mention

is made to using other intein sequences from other organisms. Given the unpredictability, as stated in the state-of-the-art, it is unclear if inteins that operate using a different mechanism than the one exemplified by Applicant, will operate as expected when the intein sequence is modified to be operable in Applicant's invention.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 6, 8, 10-11, 15, 20, 22, and 24-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Xu et al (1996, The EMBO Journal 15(19):5146-5153; listed in IDS) in view of Xu et al (1993 Cell 75:1371-1377).

The claims are drawn to a DNA construct, or a method for expressing multiple genes in cells comprising a DNA construct, comprising a single promoter at the 5' end, multiple genes or exteins encoding one or more proteins, one or more intein sequences, and transcription termination sequences, wherein at least one of the intein sequences can catalyze excision of the exteins and wherein the excised exteins are not ligated, or wherein the DNA construct encodes a glycine or alanine linking the intein and extein amino acid sequences.

Xu et al (1996) in view of Xu et al (1993) teach a DNA construct comprising a nucleic acid sequence encoding the Pyrococcus GB-D DNA polymerase intein operably associated at the 3' end of the nucleic acid encoding the maltose binding protein and with a nucleic acid sequence encoding the paramyosin delta-Sal operably associated at its 3' end with the Pyrococcus GB-D DNA polymerase intein (Xu et al, 1993; page 1371, right column, 1st paragraph of Results). Xu et al (1996) teach changing the coding of Ser538 to an alanine cause the two proteins to be

excised but not ligated together (page 5148, Table II). Xu et al (1993) also teach the incorporation of an isopropyl beta-D-thiogalactoside inducible promoter operably linked to the above nucleic acid sequence encoding the maltose binding protein::Pyrococcus GB-D DNA polymerase intein::paramyosin delta-Sal polypeptide (page 1376, left column, 2nd paragraph). It would be inherent for the construct to include a transcription termination sequence and as such, Xu et al (1996) in view of Xu et al (1993) anticipate the claimed invention.

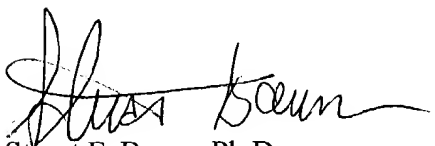
8. Claims 2, 7, 9, 12-14, 16, 18, 21, 23, and 26-29 are deemed free of the prior art, given the failure of the prior art to teach or reasonably suggest a DNA construct for expression in eucaryotic cells or method for expressing multiple genes in eucaryotic cells comprising a DNA construct comprising a promoter, multiple genes or exteins encoding one or more proteins, one or more intein sequences fused to the carboxy-terminus portion of each gene except the last gene to be expressed and a transcription termination sequence, and wherein the genes encoding one or more proteins are preceded or followed by a sequence encoding a peptide that targets the gene expression product to a particular compartment within the cell, or wherein the construct is expressible in plants and wherein the proteins are selected from the groups in claims 12, 13, 14, 26, 27, or 28.

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stuart F. Baum whose telephone number is 571-272-0792. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Stuart F. Baum Ph.D.
Patent Examiner
Art Unit 1638
March 3, 2004